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Case Report

Thyroiditis After COVID-19 mRNA Vaccine: A Case Series

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ABSTRACT

Background: Although SARS-CoV-2 virus infection has been reported to cause subacute thyroiditis, the mRNA vaccine for SARS-CoV-2 is suspected to induce thyroiditis with thyrotoxicosis.
Case Report: : We describe 3 patients with no history of thyroid disease who presented with symptomatic, biochemical, and radiological evidence of thyroiditis with thyrotoxicosis, 10 to 20 days after receiving either Pfizer Bio-NTech or Moderna COVID-19 mRNA vaccines. All patients presented with thyrotoxicosis but with negative thyroid-stimulating immunoglobulins for Graves disease and no autonomous nodules. Two patients underwent thyroid uptake scans that confirmed thyroiditis. One patient had significantly increased erythrocyte sedimentation rate and interleukin-6. All patients showed improvement in symptoms with nonsteroidal anti-inflammatory drugs, and 1 patient eventually required steroids for symptom control.
Discussion: The mRNA vaccine for SARS-CoV-2 was associated with thyroiditis and led to thyrotoxicosis. Elevated proinflammatory markers and cytokines after vaccines may play a major role.
Conclusion: Our case series report highlights a possible relationship between the COVID-19 mRNA vaccine and thyroiditis with thyrotoxicosis, which has not been recognized by health providers.

Introduction

Subacute thyroiditis (SAT) is an inflammatory disease of the thyroid and a common cause of thyrotoxicosis. It is normally characterized by an enlarged tender thyroid gland with referred pain to the jaws and the ear; biochemical evidence of thyrotoxicosis; elevated inflammatory markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein; and decreased radioactive iodine uptake. It is usually caused by infections with various viruses.[1] More recently, there has also been a case report of SAT due to the SARS-CoV-2 infection.[2]

Although viruses are the main etiology of SAT, there have been a rare case reports of SAT following immunizations, such as the influenza vaccine.[3] These rare cases have been reported so far only in patients receiving immunizations containing viral antigens. Recently, 2 pharmaceutical companies, Pfizer Bio-NTech and Moderna, developed mRNA vaccines for SARS-CoV-2. Unlike the influenza vaccine, which directly exposes the body to viral antigens, mRNA vaccines work by instructing the cells to synthesize viral proteins and thereby trigger the immune system to produce antibodies. With the universal use of mRNA vaccines, their possible side effects will be discovered. SAT induced by mRNA vaccines for SARS-CoV-2 has been recently reported but is not well-recognized.[4,5] We report 3 cases of thyroiditis with thyrotoxicosis following the mRNA vaccine for SARS-CoV-2.

Case Report

Patient 1

A 37-year-old Indian man with a history of prediabetes and dyslipidemia presented to the emergency department with fever and neck pain. The patient had received his first dose of Moderna mRNA COVID-19 vaccine approximately 15 days before the presentation. In the emergency department, his vital signs were significant for tachycardia, with a heart rate of 125 beats/min. Physical examination was significant for an enlarged, tender thyroid gland, without proptosis. The emergency department work-up also

Abbreviations: ESR, erythrocyte sedimentation rate; SAT, subacute thyroiditis.

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Table
Demographic Characteristics, Laboratory Results, and Imaging Findings of the 3 Patients

Characteristics	Patient 1	Patient 2	Patient 3
Age, years	37	35	41
Sex	Male	Male	Female
Body mass index, kg/m^2	26	28.4	21
COVID-19 vaccine	Moderna	Pfizer-BioNTech	Pfizer-BioNTech
Onset of symptoms	15 days after the first dose	10 days after first dose	20 days after the second dose
Heart rate, beats/min	125	130	110
Treatment	Propranolol, ibuprofen, and prednisone	Propranolol and ibuprofen	Cardizem and ibuprofen
TSH, mIU/mL (NR: 0.45-4.5 mIU/mL)	<0.01	0.07	0.019
Free thyroxine, ng/dL (NR: 0.82-1.77 ng/dL)	6.96	3.04	2.52
Total triiodothyronine, ng/dL (NR:76-181 ng/dL)	328	200	233
TSI	Negative	Negative	Negative
TPO	Negative	Negative	Negative
Antithyroglobulin	Negative	Negative	Negative
ESR, mm/h (Reference: 0-10 mm/h)	51	NA	NA
Interleukin-6, pg/mL (NR: ≤1.8 pg/mL)	13.2	NA	NA
Radioactive iodine thyroid uptake scan	4-hour, 0.4%	NA	4-hour, 1.4%
(NR: 4-hour, 5-15%; 24-hour, 15%-35%)	24-hour, 0.01%		24-hour, 0.6%

Abbreviations: ESR = erythrocyte sedimentation rate; NA = not available; NR = normal range; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone; TSI = thyroid-stimulating immunoglobulin.

showed significantly increased ESR and interleukin-6 level, with negative COVID-19 polymerase chain reaction test. While presenting as hyperthyroid, he underwent a radioactive iodine uptake scan that showed a decreased uptake, with a 4-hour uptake of 0.4% and a 24-hour uptake of 0.01%, consistent with thyroiditis. The patient was initially started on treatment with propranolol and ibuprofen. However, after 3 days, his symptoms of neck pain continued; therefore, ibuprofen was discontinued, and prednisone was tapered, which subsequently alleviated his symptoms.

Patient 2

A 35-year-old Indian man with unremarkable medical history presented to the clinic with complaints of palpitations and neck pain. He had received his first dose of Pfizer-BioNTech mRNA COVID-19 vaccine approximately 10 days before the presentation. Physical examination was significant for tachycardia, with a heart rate of 130 beats/min and anterior neck tenderness. He was started on propranolol and ibuprofen, which alleviated his symptoms. Two weeks after the initial visit, repeat thyroid function tests showed improvement, with trending down free thyroxine and total triiodothyronine, without any thyroxine production inhibition therapy, suggesting a clinical diagnosis of SAT.

Patient 3

A 41-year-old Indian woman with an unremarkable past medical history was referred to the endocrinology department for hyperthyroidism and tachycardia. She had received her second dose of Pfizer-BioNTech vaccine 20 days before. She recalled no other symptoms except palpitations after the first dose; however, she reported worsened palpitations after the second dose. In the clinic, she was found to be tachycardic, with a heart rate of 110 beats/min. The radioactive iodine thyroid uptake scans revealed a 4-hour uptake of 1.4% and a 24-hour uptake of 0.6%, suggestive of thyroiditis. She was managed with diltiazem and ibuprofen.

The laboratory findings showed normal complete blood count and comprehensive metabolic panel for all 3 patients. Additional laboratory results, including thyroid-stimulating hormone, free thyroxine, total triiodothyronine, and ESR, are shown in the Table. Thyroid antibodies, including thyroid-stimulating immunoglobulin, thyroid peroxidase, and antithyroglobulin, were negative (Table). Thyroid ultrasound in all 3 patients showed a heterogeneous and enlarged thyroid gland without nodules (Fig.).

Discussion

Cases of patients who developed SAT after SARS-CoV-2 mRNA vaccine have recently been reported.[4,5] İremli et al[4] reported cases of 3 women who developed SAT a few days after mRNA vaccines for COVID-19 in Europe, whereas Schimmel et al[5] reported 1 similar case in the United States. The common clinical features are middle age, no history of thyroid disease, development of thyrotoxicosis with neck tenderness 4 to 27 days after the first or second dose, and negative thyroid antibodies (thyroid-stimulating immunoglobulin, thyroid peroxidase, and antithyroglobulin). Thyroid ultrasound showed enlarged heterogeneous thyroid glands with no nodules and decreased uptake.

Patients with SAT typically present with neck tenderness caused by thyroid gland inflammation. The key clinical features of SAT are elevated levels of ESR and C-reactive protein and neck pain that is relieved by nonsteroidal anti-inflammatory drugs or steroids.[6] Additionally, color flow Doppler ultrasonography of the thyroid gland shows an enlarged heterogeneous gland with low to normal vascularity.[7] Another hallmark of the disease is a low thyroid uptake of radioactive iodine. The peak incidence occurs around 30 to 50 years of age, and women are more frequently affected than men.[8] A previous study has also shown the susceptibility of SAT in patients with certain types of human leukocyte antigen such as HLA-B35.[9]

Our 3 middle-aged patients, 2 men and 1 woman, developed symptomatic hyperthyroidism with biochemical evidence of thyrotoxicosis after receiving either Moderna or Pfizer-BioNTech vaccines within 10 to 20 days after the first or second dose. Work-up for Graves disease and autonomous nodule was negative. Patients 1 and 3 had decreased radioactive iodine uptake scans, which confirmed thyroiditis, for which the differential diagnosis includes SAT and Hashitoxicosis. Although all 3 patients had negative thyroid peroxidase and antithyroglobulin, there is still a small possibility that they may have had baseline antibody-negative chronic thyroiditis exacerbated by the COVID-19 mRNA vaccine.

The mechanism by which the vaccine causes thyroiditis remains unclear due to limited data. Although immune reactivity to viral antigens has been thought to be a plausible mechanism in cases of SAT following influenza vaccinations, there may be a different mechanism at play in patients who receive mRNA vaccinations. In a prior single-center study, patients infected with SARS-CoV-2 who developed thyrotoxicosis were found to have elevated interleukin-6 levels.[10] This study indicated that COVID-19 may be associated with a high risk of thyrotoxicosis, in relationship with systemic

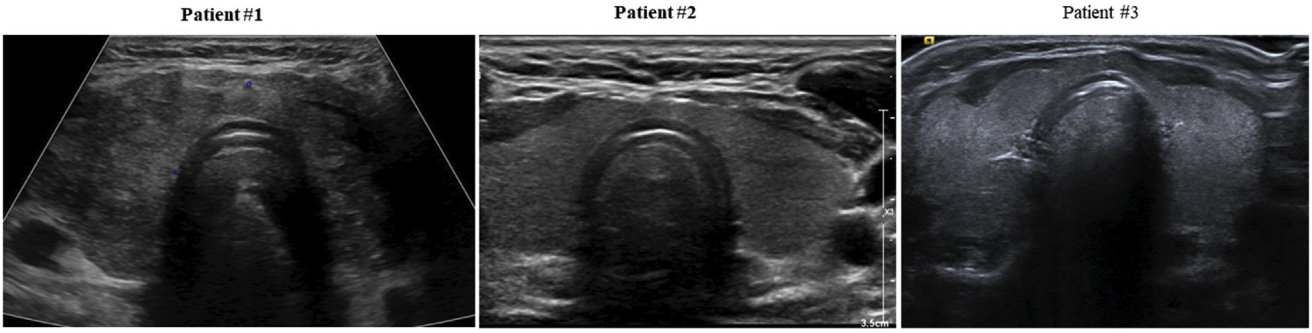

Fig. Transverse ultrasound images of the thyroid gland of the 3 patients showing a heterogeneous and enlarged thyroid gland without nodules.

immune activation and cytokine storm induced by the SARS-CoV-2 infection. A previous report has also shown interferon and ribavirin therapy–induced thyrotoxicosis.[11] In our study, patient 1 had a significantly increased interleukin-6 level, suggesting a possible role of cytokines in the mRNA vaccine–induced SAT.

Our cases showed that the latency period is about 10 to 20 days after the vaccine injection (first or second), and we will follow-up to monitor the disease course for the hyperthyroidism, hypothyroidism, and recovery phases. It is unclear whether mRNA-induced SAT has a different disease course compared with other common virus-induced SAT.

Although most cases of SAT are self-limiting, the recommended approach is to start symptomatic therapy for heart rate control, with nonsteroidal anti-inflammatory drugs as needed for neck pain in mild cases and steroids reserved for severe cases.[12] Although specific data on the efficacy of COVID-19 vaccines in the setting of glucocorticoids administration are lacking, studies have shown a decreased efficacy of other virus vaccines, like the influenza vaccine, after glucocorticoid administration.[13] In mRNA vaccine administration, the expressed S antigen (spike protein) elicits immune responses, including both antibody and T-cell responses, to protect against COVID-19; however, systemic glucocorticoids have been considered as immunosuppressive therapy, which can suppress T-helper cells, which modulate antibody class switching.[14,15] Haynes and Fauci[16] found that intravenous hydrocortisone (400 mg) administration decreased the circulation of T-cells within 48 hours. Therefore, for those patients with mRNA vaccine–induced SAT, glucocorticoids should be used with caution, as they might interfere with the protective antibody production induced by vaccinations.

In addition, it is unclear whether the mRNA vaccine–induced SAT is associated with younger age since data from the age group of 12 to 16 years are limited. The mRNA vaccine has been approved for adolescents (12-16 years) by the US Food and Drug Administration. In this age group, the thyroid hormone plays a critical role in physical growth and sexual/mental development. Undiagnosed thyroiditis may cause certain medical, psychological, and social disorders that affect growth and development during puberty.[17] The potential effects of the mRNA vaccine on adolescent growth and development are unknown; therefore, health care providers' index of suspicion and patients' education are important.

A limitation of our series is the small number of patients. It would be interesting to see the incidence of this phenomenon in the future as more people start getting SARS-CoV-2 vaccines.

Conclusion

In summary, we reported 3 cases of thyroiditis with thyrotoxicosis that occurred 1 to 4 weeks after receiving the first or second dose of the mRNA COVID-19 vaccines, indicating a possible relationship between SAT and mRNA COVID-19 immunization. Beta-blockers and nonsteroidal anti-inflammatory drugs are usually recommended to control the symptoms, as glucocorticoids might interfere with the vaccine-induced protective antibody production. With an increase in the number of immunizations, further data will provide more insight for future clinical care decisions.

Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Desailloud R, Hober D. Viruses and thyroiditis: an update. *Virol J*. 2009;6:5.
2. Brancatella A, Ricci D, Viola N, Sgrò D, Santini F, Latrofa F. Subacute thyroiditis after Sars-COV-2 infection. *J Clin Endocrinol Metab*. 2020;105(7).
3. Altay FA, Güz G, Altay M. Subacute thyroiditis following seasonal influenza vaccination. *Hum Vaccin Immunother*. 2016;12(4):1033–1034.
4. İremli BG, Şendur SN, Ünlütürk U. Three cases of subacute thyroiditis following SARS-CoV-2 vaccine: postvaccination ASIA syndrome. *J Clin Endocrinol Metab*. 2021;106(9):2600–2605.
5. Schimmel J, Alba EL, Chen A, Russell M, Srinath R. Letter to the Editor: thyroiditis and thyrotoxicosis after the SARS-CoV-2 mRNA vaccine. *Thyroid*. 2021;31(9):1440.
6. Pearce EN, Bogazzi F, Martino E, et al. The prevalence of elevated serum C-reactive protein levels in inflammatory and noninflammatory thyroid disease. *Thyroid*. 2003;13(7):643–648.
7. Hiromatsu Y, Ishibashi M, Miyake I, et al. Color Doppler ultrasonography in patients with subacute thyroiditis. *Thyroid*. 1999;9(12):1189–1193.
8. Volpé R. Subacute thyroiditis. *Prog Clin Biol Res*. 1981;74:115–134.
9. Ohsako N, Tamai H, Sudo T, et al. Clinical characteristics of subacute thyroiditis classified according to human leukocyte antigen typing. *J Clin Endocrinol Metab*. 1995;80(12):3653–3656.
10. Lania A, Sandri MT, Cellini M, Mirani M, Lavezzi E, Mazziotti G. Thyrotoxicosis in patients with COVID-19: the THYRCOV study. *Eur J Endocrinol*. 2020;183(4):381–387.
11. Lin YQ, Wang X, Murthy MS, Agarwala S. Life-threatening thyrotoxicosis induced by combination therapy with PEG-interferon and ribavirin in chronic hepatitis C. *Endocr Pract*. 2005;11(2):135–139.
12. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid*. 2016;26(10):1343–1421.
13. Sytsma TT, Greenlund LK, Greenlund LS. Joint corticosteroid injection associated with increased influenza risk. *Mayo Clin Proc Innov Qual Outcomes*. 2018;2(2):194–198.
14. Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. *Nature*. 2020;586(7830):594–599.
15. Liberman AC, Budziñski ML, Sokn C, Gobbini RP, Steininger A, Arzt E. Regulatory and mechanistic actions of glucocorticoids on T and inflammatory cells. *Front Endocrinol (Lausanne)*. 2018;9:235.
16. Haynes BF, Fauci AS. The differential effect of in vivo hydrocortisone on the kinetics of subpopulations of human peripheral blood thymus-derived lymphocytes. *J Clin Invest*. 1978;61(3):703–707.
17. Hanna CE, LaFranchi SH. Adolescent thyroid disorders. *Adolesc Med*. 2002;13(1):13–35. v.